16. (new) The process according to one of Claim 11 wherein said process is carried out at a pH of from 5 to 10.---

REMARKS

Claims 1-6 are pending in the application. Claims 1-6 are rejected under 35 U.S.C. § 112, first paragraph. Claims 1-3 are rejected under 35 U.S.C. §103. Applicants have canceled claims 1-6 and replaced them with new claims 8-16 which more particularly point out and distinctly claim the invention. No new matter is introduced by the new claims and the claims are fully supported by the instant specification. For reasons detailed below, the rejections should be withdrawn and the claims allowed to issue. Entry of the foregoing amendments is respectfully requested.

1. The Rejections Under 35 U.S.C. § 112

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph. The Examiner alleges that the claimed subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

According to the Examiner, the invention appears to employ a novel strain of *E. coli* to obtain a specific product. The written description of that strain and the method of isolating is insufficiently reproducible. The specification discloses at page 7 that suitable strains were deposited at DSM under Budapest Treaty conditions.

Applicants aver that the deposited material referred to on page 7, *i.e.*, DSM 11902 and DSM 12566 has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the purpose of Patent Procedure and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent.

Additionally, Applicants direct the Examiner's attention to page 7, lines 15-29, which identify the deposited organisms by deposit accession number, date of deposit, name and address of the depository and the complete taxonomic description.

Claims 1-6 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, (i) claim 1 is said to be confusing in the recitation of "coded for an enzyme";(ii) claim 3 fails to find proper antecedent basis in claim 1 for "genes that are coded for an enzyme" and it is unclear whether one gene or more genes are involved in coding for the required enzyme;(iii) claims 1-6 are incomplete in the absence of a recovery step for the product produced; (iv) the term "generic" in claim 1 appears to be redundant; and (v) claims 5 and 6 are in improper form because a multiple dependent claim may not depend on another multiple dependent claim.

Applicants have canceled claims 1-6 and replaced them with new claims 8-16. The new claims have been written to address each of the issues raised by the Examiner. In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C.§112 be withdrawn.

2. The Claims are not Obvious

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kula *et al.* (U.S. Patent No. 5,523,223;"Kula") taken with Kita *et al.* (1996, Applied and Environmental Microbiology 62:2303-2310;"Kita") and Texidre et al. (EP0736606 A1;"Tixidre").

According to the Examiner, Kula teaches a process for the production of 3(R) hydroxybutyric acid derivatives using a microbial strain having reductase activity. The Examiner maintains that although the reference differs from the claimed invention in that it does not use an *E. coli* strain transformed with a gene coding for a suitable reductase, Kita teaches the production of an *E. coli* strain transformed with a gene coding for a reductase which is suitable for converting related 3-(R)-hydroxybutyric acid derivatives.

The Examiner alleges that one of ordinary skill in the art would have had a reasonable expectation of success in obtaining 4,4,4 trifluoro-3(R) –hydroxybutyric acid derivatives using the microbial strain having reductase activity as taught by Kula and Kita. Further, one of ordinary skill in the art would have had been motivated at the time the claimed invention was made to produce the trifluoro derivatives of 3(R) –hydroxybutyric acid in view of the teachings of Tixidre regarding the utility of such compounds as intermediaries in the production of befloxatone, a compound having important pharmaceutical activity as a reversible and selective monoamine oxidase-A inhibitor.

A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art provides one of

ordinary skill in the art with a reasonable expectation of success. *In re Ofarrell* 853 F.2d 894 (Fed. Cir. 1988).

The present invention is not rendered obvious by the cited references either alone, or in combination, for reasons detailed below.

First, Kula describes a reductase from *Canidida parapsilosis* having an extremely broad substrate spectrum. Applicants assert that based on the unpredictability of biological systems, one skilled in the art would not have had a reasonable expectation that such a reductase of *Canidida parapsilosis* could be successfully cloned and expressed in *E.coli.*

Second, although Kita describes microorganisms of the genus *Escherichia* transformed with a gene encoding a reductase from *Sporobolomyces salmonicolor,* Kita only demonstrates the use of the substrate ethyl 4-chloro-3-oxobutanoate. Kita fails to demonstrate that such a reductase is capable of reducing the (R)-4,4,4-trifluoro-3-hydroxybutyric acid specified in claim 1. Thus, neither Kita, nor Kula, either alone or in combination disclose or suggest , ***Escherichia coli*** expressing a reductase capable of reducing **(R)-4,4,4-trifluoro-3-hydroxybutyric acid**.

In view of the foregoing, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

Entry of the foregoing remarks into the file history of the above identified application is respectfully requested. Applicants believe that the invention described and defined by the claims

is patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the claims is requested. An early allowance is earnestly sought.

Applicants submit herewith as attached APPENDIX A, a marked-up version of the claims to show all changes relative to the previous claims.

Respectfully submitted,

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APPENDIX A

IN THE SPECIFICATION

Please delete the first paragraph of the specification and replace it with the following paragraph:

The invention relates to a novel biotechnological process for preparing [trifluro-3(R)-hydroxybutyric acid] 4,4,4-trifluoro-3(R)-hydroxybutyric acid derivatives of the general formula

[Trifluro-3(R)-hydroxybutyric acid] 4,4,4-trifluoro-3(R)-hydroxybutyric acid derivatives such as ethyl 4,4,4-trifluoro-3(R)-hydroxybutyrate are important intermediates for preparing Befloxatone, a monomine oxidase A inhibitor (EP-A-0 736 606).

On page 2, replace the paragraph on line11-29, with the following paragraph:

According to the invention, the process is carried out by a trifluoroacetoacetic acid derivative of the general formula

in which

R1 is $-OR^2$, in which R^2 is hydrogen, C_{1-10}-alkyl, [C_{1-10}-alkenyl] C_{2-10}-alkenyl, C_{3-8}-cycloalkyl, aryl, alkoxyalkyl or alkoxyalkoxyalkyl,

$-NR^3R^4$, in which R^3 and R^4 are identical or different and represent

hydrogen, C_{1-10}-alkyl C_{2-10}-alkyl, [C_{1-10}-alkenyl] C_{2-10}-alkenyl, C_{3-8}-cycloalkyl or aryl,

or

-SR^5, in which R^5 is hydrogen, C_{1-10}-alkyl, [C_{1-10}-alkenyl] C_{2-10}-alkenyl, aryl or C_{3-8}-cycloalkyl,

being converted by means of microorganisms which are able to reduce a carbonyl function, or by means of a cell-free enzyme extract of these microorganisms, into the compound of the general formula

in which R^1 has the same meaning.

On page 3, replace the paragraph on lines 3-5, with the following paragraph:

Ethenyl, propenyl, allyl, and butenyl can, for example, be used as [C_{1-10}-alkenyl] C_{2-10}-alkenyl. Allyl is preferably used.

IN THE CLAIMS

Please cancel claims 1-7 and replace them with new claims 8-15.

---8. (new) A process for preparing trifluoro-3(R)-hydroxybutyric acid derivatives of the general formula

wherein

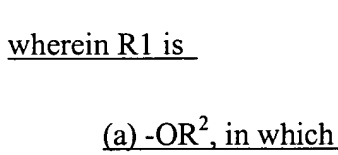
R1 is (a) -OR^2, in which R^2 is hydrogen, C_{1-10}-alkyl, C_{2-10}-alkenyl, C_{3-8}-cycloalkyl, aryl, alkoxyalkyl or alkoxyalkoxyalkyl,

(b) -NR^3R^4, in which R^3 and R^4 are identical or different and represent hydrogen, C_{1-10}-alkyl, C_{2-10}-alkenyl, C_{3-8}-cycloalkyl or aryl, or

(c) -SR^5, in which R^5 is hydrogen, C_{1-10}-alkyl, C_{2-10}-alkenyl, aryl or C_{3-8}-cycloalkyl,

which process comprises:

(i) reacting a trifluoroacetoacetic acid derivative of the general formula



wherein R1 is

(a) -OR^2, in which R^2 is hydrogen, C_{1-10}-alkyl, C_{2-10}-alkenyl, C_{3-8}-cycloalkyl, aryl, alkoxyalkyl or alkoxyalkoxyalkyl,

(b) -NR^3R^4, in which R^3 and R^4 are identical or different and represent hydrogen, C_{1-10}-alkyl, C_{2-10}-alkenyl, C_{3-8}-cycloalkyl or aryl, or

(c) -SR^5, in which R^5 is hydrogen, C_{1-10}-alkyl, C_{2-10}-alkenyl, aryl or C_{3-8}-cycloalkyl,

using microorganisms of the genus *Escherichia*, or cell-free extracts derived therefrom, wherein said microorganisms express an enzyme which is capable of reducing a carbonyl function; and

(ii) isolating said trifluoro-3(R)-hydroxybutyric acid derivatives.

8. (New) The process according to Claim 7 wherein the microorganisms of the genus *Escherichia* are transformed with a gene encoding an enzyme which is capable of reducing a carbonyl function.

10. (New) The process according of Claim 9 wherein the microorganisms of the genus *Escherichia* are selected from the group consisting of *Escherichia coli* JM109, HB101 or DH5.

11. (New) The process according to Claim 9 or 10 wherein the microorganisms of the genus *Escherichia coli* are transformed with a gene encoding a glucose dehydrogenase.

12. (New) The process of Claim 11 wherein the microorganisms of the genus *Escherichia* are transformed with the plasmids pKAR and pKKGDH, as deposited under the deposition numbers DSM 11902 and DSM 12566, respectively.

13. (New) The process of Claims 8, 9, 10 or 12 wherein said process is carried out a temperature of from 5 to 60°C.

14. (New) The process of Claim 11 wherein said process is carried out a temperature of from 5 to 60°C.

15. (new) The process according to one of Claims 8, 9, 10 or 12, wherein said process is carried out at a pH of from 5 to 10.

16. (new) The process according to one of Claim 11 wherein said process is carried out at a pH of from 5 to 10.---